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TYPHOID FEVER

A Review of 68 Cases at Children's Hospital from 1937 to 1947

Lars Lundgoot, M.D.

Historical Introduction: Typhoid fever was probably first recognized by Willis in 1643. Chomel in 1821 described intestinal ulcers in the region of the cecum while Nathan Smith in 1830 recognized the contagiousness of the disease. The true nature of the disease was clarified by the discovery of the typhoid bacillus by C. J. Eberth in 1880. Pfeiffer isolated the organism in 1884 and Hyeppe recovered the organism from the urine in 1886; Neuhauss was the first to obtain a positive blood culture. The serum diagnosis of the disease was introduced by Widal in 1896.

Inoculation against typhoid was carried out experimentally by Chautemisse and Widal in 1888 and by Wright in 1896; the latter first used typhoid vaccine prophylactically in man, his subjects being English soldiers. Colonel Russell introduced compulsory vaccination against typhoid into the U. S. Army in 1911, thue materially reducing the morbidity and mortality from this disease.

Typhoid fever has shown a steady decline in the number of cases reported from the various communities of the United States during the past few decades. It appears from the literature that in infants the symptoms are more variable than in older children and adults, that the course is shorter but the mortality is higher. In 1912 Griffith in a review of the literature reported 278 cases under 2½ years of age with a mortality of 57%. Previously Henock in 1875 had reported 375 cases in infants and children with typhoid fever with a mortality of 14%; Blackader in 1900 on the other ha nd reported 100 cases in which only one patient died. From these reports it appears that the mortality statistics vary within wide limits and depend upon the virulence of the disease and the previous health and resistance of the child.

Statistics show that the disease is not of frequent occurrence in infants and children since they are less likely to be exposed, although they are not known to possess immunity. Only a few reports which contribute to a clearer understanding of the disease in childhood have appeared in American medical literature.

From 1937 to 1947, 68 cases of typhoid fever were seen at Children's Hospital and a tabulation of its yearly and monthly incidence is noted in Table 1.

These figures are in keeping with the general impression that typhoid is essentially an autumnal fever with more than half of our cases occurring in

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July, August, September and October, although it may occur at any time during the year.

Only 9 (or 13 percent) of the cases in this series entered the hospital with a possible diagnosis of typhoid fever. The remaining patients were variously diagnosed as acute pharyngitis, acute otitis media, gastritis, enteritis, bronchitis, pneumonia, pyelitis, poliomyelitis, rheumatic fever, influenza, possible meningitis and appendicitis. The racial and sex distribution is noted in Table 2.

TABLE 1

YEAR	CASES	%	MONTH	CASES	%
1937	8	12	January	3	5
1938	8	12	February	5	7
1939	3	5	March	1	2
1940	8	12	April	3	5
1941	7	10	May	7	10
1942	5	7	June	1	2
1943	4	6	July	8	12
1944	8	12	August	15	22
1945	7	10	September	11	16
1946	10	15	October	4	6
			November	0	7
			December	5	7

TABLE 2

	NUMBER OF CASES	PERCENTAGE
White females	15	22
White males	16	24
Colored females	17	25
Colored males	20	30

A positive diagnosis of typhoid fever was made in 43 cases or 63% by demonstrating the organism in blood, stool and urine cultures.

Blood cultures are of most value in early diagnosis and positive cultures are said to be obtained in about 90% of cases during the first week of the disease. As the infection progresses and localizes, however, the percentage drops to about 75 percent by the second week and to about 30 percent in the third week. In the present series only 25 cases, or 44 percent, had a positive blood culture. This low figure is probably dependent upon the fact that the patient often did not enter the hospital until late in the course of the disease or that the disease was not suspected early. In only 12 cases was a

positive blood culture found in the first week, eight in the second and five in the third week.

With stool cultures only 10 to 15 percent are likely to be positive during the first 10 days of the disease. Thereafter, the percentage rapidly increases reaching about 50 percent by the third week and 80–90 percent during convalescence. In this series, positive stool cultures were found in 32 cases or 49 percent. In only ten cases was a positive stool found during the first week, ten in the second week, six in the third, and six in the fourth week.

Typhoid bacilli do not ordinarily occur in the urine until after the second week of the disease, when only 25 to 30 percent of the cases are reported to be positive. Bacteriological examination of the urine, therefore, is not ordinarily required nor indicated for diagnostic purposes. In our series urine cultures were obtained in 41 cases and of these 15% showed a positive culture.

In 25 cases (30%) the organism was not demonstrable either in the blood, stool or urine but a positive Widal in titer of 1/160 or above was obtained with O and H antigen. This dilution or higher is usually indicative of typhoid fever in the majority of cases. The sera of normal individuals who have never had typhoid or vaccinations against the disease may rarely agglutinate the H and O antigens up to this level, but it is usually in lower titers of 1/20 to 1/40.

A positive Widal agglutination was found in 66 out of the 68 cases. In one the Widal was not taken as the patient had a positive blood culture. In the second case the Widal was negative, but blood and stool cultures were positive. In this instance the Widal was taken during the first week of the disease and was not repeated at a later date.

A positive Widal reaction can usually be obtained at the end of the first week with a rising titer as the disease progresses. It is claimed that it may be delayed however for 6 to 7 weeks or until the symptoms of the disease have disappeared. This was not the case in our series. A single negative test should not necessarily exclude the diagnosis of typhoid fever, and repeated tests should be made during the course of the disease.

The serum of a typhoid patient may be amnestic and agglutinate a culture of para-typhoid bacilli and vice-versa. This reaction was present in 30% of our cases. This was also found to be true in our tularemia cases which gave a positive Widal agglutination along with a positive agglutination for the bacterium tularense. A positive Widal reaction is usually present in carriers and also in those who have had prophylactic typhoid vaccination, and may persist for some time.

The compliment fixation test for typhoid was not done in any of our cases. Available data indicate that it may be superior to the Widal in

specificity and sensitivity. Owing to the popularity and greater simplicity of the Widal, it has never received much attention in the serum diagnosis of the disease. The test is less likely to give false positive or amnestic reactions. About 50 percent of cases of typhoid give positive complement fixation test reactions between the first and second weeks of the disease and between 90 to 95 percent after the second week. Garbat has also observed that the sera of about 85 percent of carriers give positive reactions six months or longer after recovery so that the compliment fixation test is also of value in aiding in the detection of carriers.

The age distribution of 68 cases of our series is noted in Table 3.

The youngest was an infant 10 months of age and the oldest was a boy 14 years of age.

TABLE 3

AGE	NUMBER OF CASES	PERCENTAGE
years		
0–1	2	3
2	11	16
3	11	16
4	13	20
5	5	8
6	5	8
7	3	4
8	4	6
9	5	8
10	1	2
11	3	4
12–14	5	8

Source of Infection: In 29 cases or 43% of this series the source of infection was indicated or strongly suspected while in 39 cases or 57% it was indeterminate since no history of the possible source was obtained. Contact with other members of the family who were carriers or who had typhoid fever was found in 11 cases. Infected well water accounted for 18 cases. In one case an outside toilet was found to be the source of infection. In another case a 12 year old boy was sent from our hospital to a convalescent home because of rheumatic heart disease. After several months his symptoms returned and the patient was again admitted to the hospital with a diagnosis of recurring rheumatic fever. The source of infection here was found to be a nurse at the convalescent home who had had typhoid fever previously and was now a carrier. Nine cases gave a history of recent vacations in the country and of drinking well water.

Onset: The progression of symptoms preceding the actual onset of the disease is very difficult to elicit in infants and children. This is dependent upon the rapidity of the invasion of the organism into the blood stream. A positive blood culture is said to be obtained in 75 to 90% of the cases during the first week and decreases after this time. This is important because a diagnosis can be made earlier by a blood culture than by any other laboratory method.

Thirty cases in this series had a more or less gradual onset having fevers for seven days or longer. One patient had fever of 3 weeks' duration prior to hospital admission. Thirty-eight cases in this series apparently became acutely ill from one to six days before admission. The period of incubation of this disease is difficult to determine as the ingestion of the typhoid bacillus and infection of the body by the organism are not synchronous. A variable interval may elapse between the entrance of the pathogenic organisms into the intestinal tract and the actual invasion of the body tissue through some portal of entry. That this interval may be indefinitely prolonged is shown in the case of healthy carriers who may harbor the bacillus for long periods. The average time for sumptoms to appear is said to be from ten to fourteen days after exposure to infection. The period may be as short as two days or as long as 23 days.

In 750 cases studied by the Spanish-American War Commission, the average incubation period was ten and one-half days, the shortest, six days.

Symptomatology: Typhoid fever is divided for convenience into weekly periods. In the average uncomplicated case, the first week is the period of invasion, during which there is a gradual increase in the severity of the symptoms. The second and third weeks correspond to the fastigium, or the period of the height of the disease. The fourth week is the period of decline. The fifth week marks the period of beginning of convalescence. This division is only arbitrary since there is a marked variability in symptoms and course of each patient. The protean manifestations presented by these 68 cases of typhoid on entrance to Children's Hospital are noted in Table 4.

It will be noted that fever was a presenting symptom in every case. Attention is directed to the frequency of sore throat, which would include pharyngitis and other signs of upper respiratory infection. Abdominal pain was also a relatively frequent presenting symptom with an incidence of 44% in the series. In one case a diagnosis of appendicitis was made on entrance to the hospital and an appendectomy was performed. At operation an apparently normal appendix was found, but some mesenteric adenitis was noted. Headache was also a rather frequent symptom and its association with some of the other manifestations was occasionally sugges-

tive of central nervous system involvement. Spinal taps were performed in 18 cases and in all instances the fluid was found to be essentially normal.

Physical signs of special interest in typhoid fever included rose spots which were present in 13 cases or 20%. No rash was noted in the remaining 80% of the cases in this series at any time. In Tice and McCreae's series where all the patients were white and were of all ages, the incidence of rose spots was found to be 80%. However, since 55% of the cases in our series were colored, it may account in part for the discrepancy. It has been stated that positive cultures can be obtained from these areas. None were taken in this series.

The spleen was found to be enlarged in 19 or 28% of our cases while tenderness upon palpation was seldom observed. In Osler's series including all ages the spleen was found palpable in 71% of the cases.

The dicrotic pulse and bradycardia which is commonly found in adults

TABLE 4

SYMPTOM	NUMBER	%	SYMPTOM	NUMBER	%
Fever	68	100	Anorexia	12	17
Sore throat	43	63	Pain in extremities	9	18
Abdominal pain	30	44	Drowsiness	6	8
Headache	22	32	Pain or stiff neck	3	4
Otitis media	21	31	Chills	3	4
Vomiting	20	29	Blood in stools	2	2
Diarrhea	19	28	Epistaxis	2	2
General malaise	17	26	Jaundice	1	1
Cough	16	23	Convulsions	1	1

was not found in this series. In 70% of the cases the pulse rates were in excess of 120 per minute at the time of admission.

In 95% of the cases the temperature was 103° or above on admission. The height of the fever was generally between 103° to 105°F. The duration and type of the fever varied considerably. Plateau and irregular temperature curves occurred with equal frequency. Both types subsided by lysis and were frequently succeeded by days or weeks during which the temperature fluctuated between 97 and 100°F. These findings correspond with Dietrich's review of 80 cases of typhoid in infants and children.

Relapses occurred in about 10% of this series. They were usually mild and ran a short course. Osler cited one case that had as many as six relapses.

One patient, a 14 month old white female infant, was hospitalized because of a continuous fever at home for 10 days. She was found to have a sore throat and bronchopneumonia together with leucopenia and splenomegaly.

The Widal with O and H antigen was at first negative but nine days later was positive in dilution up to 1 to 80. The blood culture was positive. She was given several blood transfusions with Rh negative blood from a soldier known to have been immunized against typhoid. The child improved slowly and was discharged after being hospitalized for thirty-seven days. Her temperature had been apparently normal for nine days prior to discharge. Five days later she was readmitted in an acute relapse with temperature of 105°F., abdominal distension and irritability. Agglutinations at the time showed O and H antigens to be positive in dilution of 1/2560 with paratyphoid "A" 1/320 and paratyphoid "B" 1/80. For five days her temperature fluctuated between 105° to 103°F. She received penicillin throughout her entire hospital course for an associated upper respiratory infection. On the sixth day a transfusion of 175 cc. of concentrated red blood cells was given to correct a rather profound associated

TABLE 5

AUTHOR	HOSPITAL	NO. OF CASES	MORTALITY
			%
Kendig and Kernae	Bellevue Hospital, N. Y. (15 year survey)	95	7
Weston and Rabill	Children's Hosp., Phila. (10 year survey)	100	8
Halperin	County Hospital, Chicago (4 year survey)	67	13
Usher	Montreal, Canada	175	6
Giampietro	Uruguay	383	8

anemia. Two hours later the temperature rose to 106° and the patient showed evidence of shock, pulmonary edema, cyanosis and an enlarged heart. She expired three hours after the transfusion. An autopsy revealed cardiac failure with dilatation of the right heart together with pleural effusion, pulmonary edema and congestion and a very large spleen. Typhoid bacilli were found in the intestinal tract, spleen and gall bladder. It was considered that the probable cause of death was due to the administration of an excessive quantity of concentrated red cells. Although often a cause of some concern, myocardial degeneration in typhoid fever is rarely a direct cause of death. The symptoms usually subside gradually and the physical signs of dilatation disappear with the subsidence of the pyrexia. It is therefore important in the later stages of a disease and during early convalescence to avoid overburdening the circulation.

The case cited above was the only death in our series or a mortality of 1.4%. This is an extremely low figure when compared to other series from other institutions as noted in Table 5.

A progressive enemia of a moderate degree was noted in practically all cases and supportive transfusions were given repeatedly as indicated.

The most characteristic blood finding in this series was a normal leucocyte count or a leukopenia. The majority of the cases showed a diminution of the polymorphonuclear cells with a relative increase in the number of lymphocytes as the disease progressed (Table 6). One patient had an associated acute bronchitis and also a gonorrheal vaginitis with a leucocytosis of 18,000. The Widal with the O and H antigen was positive in a 1/320 dilution. The second case had a complicating acute iritis with a tonsillitis and diarrhea with a leucocytosis of 15,400. The Widal with the O and H antigen was positive to 1/320. Cultures of the blood and stool were negative. The third case had an acute bilateral otitis media with symptoms of a generalized sepsis. The Widal with the O and H antigens was positive to 1/640 with a rising titer in one week to 1/2560. The blood and stool cultures were negative. The leucocyte counts in these three cases fell rapidly as the complications were brought under control.

TABLE 6

NUMBER OF LEUKOCYTES	NUMBER OF CASES	PERCENTAGE
5000 and under	12	18
5000 to 7500	27	40
7500 to 10,000	26	37
10,000 and higher	3	4
Total	68	

Mild uncomplicated cases ran their course on an average of 10 days The severe cases were protracted for many weeks or months. The average over-all hospital stay of the cases in this series was twenty-one days. Although typhoid fever is a relatively infrequent disease in infants and children, it should be borne in mind. A persistent fever combined with an enlarged spleen and typical rose spots form a good clinical diagnostic triad. Notwithstanding the value of the clinical signs, the specific recognition of the disease depends upon the isolation of the typhoid bacilli from the blood, stool, urine, rose spots or other secretions. The Widal and complement fixation tests are further aids as is the blood picture of leucopenia with a relative increase in large lymphocytes. Only by a careful analysis and exclusion and the early resort to laboratory aids can the diagnosis of typhoid fever be confirmed.

Practically every organ and tissue in the body may be the seat of secondary pathologic processes. Twenty-two patients in this series or 32% had some complications as noted in Table 7.

Suppurative processes as manifested by otitis media, furunculosis, and

acute mouth infections were most common. Bronchopneumonia occurred in four patients.

Treatment: Prophylaxis is of the utmost importance. Typhoid fever is a preventable disease and should be eliminated by adequate sanitation, especially supervision of the water supply and removal of any possible sources of infection, segregation of typhoid patients and also by anti-typhoid vaccination.

The active treatment of all the patients in this series was essentially supportive and symptomatic with the administration of high caloric, low residue diets. In toxic cases the maintenance of proper electrolyte balance by the infection of parenteral fluids was an important consideration. In cases with high fever, aspirin, tepid and cool sponges, alcohol rubs and colonic irrigations were given. Constipation was controlled by mineral oil and enemas. In cases with diarrhea, a high protein, low fat diet was

TABLE 7

COMPLICATION	NUMBER OF CASES	PERCENTAGE
Suppurative otitis	6	10
Bronchopneumonia	4	6
Acute mouth infection	4	6
Furunculosis	3	4
Pyelitis	2	3
Pansinusitis	2	3
Acute iritis	1	1
Total	22	

prescribed. In some instances lactic acid skimmed milk was given and frequently reinforced with proteins. Blood transfusions were given for the correction of anemia and to supply fresh complement. Sulfadiazine was given in adequate doses at the onset of the disease in thirty-three cases with no appreciable effect. Penicillin was given in eight cases similarly with no demonstrable effect. In three cases both sulfadiazine and penicillin were given but failed to modify the course of the disease. In one case streptomycin was given in adequate doses for 7 days and discontinued when it was found to have no particular value. In this regard, streptomycin has not been found to be effective in the treatment of either typhoid fever or typhoid carriers. In the report of the Committee on Chemotherapeutics and Other Agents, 51 cases of typhoid fever were treated with streptomycin for 7 to 8 days with a dose of about 4 grams in the majority of instances. No favorable effect on the course of the disease was noted. Combined oral and intramuscular administration seemed to offer no advantage over the intramuscular route alone.

Bacteriophage in the treatment of typhoid fever was reported on recently by Knouf and his coworkers in California. They have used the drug for the past ten years. During the first four years an unselected stock bacteriophage was used with varying results, some patients reacting, others deriving no effect, some having a modified course and others a bacteriologic and clinical recovery. This prompted a search for the unknown factor in bacteriophage itself. The present concept of the nature of these virus-like agents is that the bacteriophages are parasites of bacteria. As a result of the work of Craigie and Yen, it is now known that a given immunologic type of bacteriophage active on Vi antigen containing E. typhosa organisms can be adapted to different types of this organism, is highly specific and exhibits the ability of lysing the organism. These investigators have treated fifty-six patients with type specific bacteriophage. Blood cultures became negative within twenty-four hours after treatment and remained negative thereafter. There was an absence of fever after treatment and immediate clinical improvement. Of this group three or 5% died. Further confirmatory work on the virtues of bacteriophage in typhoid fever is awaited with interest.

SUMMARY

Sixty-eight cases of typhoid fever in children have been reviewed. A positive diagnosis was obtained in forty-three cases or 63% by demonstrating the organism in cultures of blood, stool or urine. In the remaining 25 cases, a positive Widal was obtained. Our mortality rate in this series was 2.3%. Treatment was largely supportive and the cases which received chemotherapy or antibiotics appeared to recover no more rapidly than the other patients in this series.

NEPHRITIS (?) IN A TWO MONTH OLD INFANT WITH CONGENITAL SYPHILIS

Case Report No. 107

John P. Jones, M.D.
Perry Gold, M.D.

R. D. 47–8656

The occurrence of albumin and red blood cells in the urine of young infants is not common. The etiology of these findings cannot always be determined, but syphilis has been observed in a certain number of cases. The scarcity of reports in the literature of nephritis in the very young prompted the following case study.

R. D., age 3 months was admitted to this hospital August 22, 1947 with the chief complaint of swelling of the hands, face, eyes and feet. The patient was well until three weeks prior to admission when the mother noticed swelling of the right eye, then the right side of the face, the right arm and foot. The mother felt that the swelling had subsided somewhat since the onset. For three weeks before admission the patient had a mucoid discharge from the nose and had become more irritable.

The past history was non-contributory. Birth weight was 8 pounds 8 ounces. The patient was breast fed and had received orange juice and cod liver oil. The family history was non-contributory.

On physical examination the temperature was 100.2° and blood pressure 128/90. The patient was well developed and fairly well nourished. He was crying and appeared irritable. Examination of the head revealed no gross abnormalities. The anterior fontanel was open. The ears were clear. The pupils were round and equal but reacted sluggishly to light. Supraorbital swelling was present on the right. The nose and mouth were normal. The chest expanded equally and the lungs were clear to percussion and auscultation. The heart was normal. The liver was felt about 1 cm. below the costal margin. Examination of the genitalia revealed both testicles descended. The scrotal sac appeared swollen and there was some excoriation over the scrotum which extended to the buttocks and perianal region. The extremities showed no paralysis or deformities. The right arm and hand appeared edematous but no pitting edema was demonstrable.

The laboratory findings were as follows: Urinalysis on August 23, 1947 showed 55 mg. albumin and many fine and coarse granular casts. Hemogram on the same day showed a hemoglobin of 9 gms., red blood count of 2,900,000, a leucocyte count of 12,000 with 15% polys and 85% lymphocytes. The total protein was 3.86 gms. per 100 cc. The Mazzini test was positive. The blood showed 320 Kahn units and quantitative Wassermann 4–4–4–4–4.

Four days later the urinalysis contained innumerable hyaline, few fine and coarse granular casts, rare red blood cells and 150 mgm. of albumin.

X-ray of the long bones showed classic evidence of moderately severe congenital syphilis.

On August 28, 1947 penicillin therapy consisting of 2,500 units every 3 hours for 14 days was begun. The patient's course while receiving penicillin was uneventful except for mild to moderately severe diarrhea which was treated with boiled skimmed milk and parenteral fluids. The blood pressure which had been recorded as 110/60 at the beginning of the penicillin treatment was down to 78/60 at the end of 14 days (September 11, 1947). The patient's edema had disappeared shortly after being admitted to the hospital. The urine on September 13, 1947, two days after completion of penicillin therapy, showed 60 mgm. of albumin, coarse granular casts and no red blood cells or white blood cells.

On September 13, 1947 the patient developed a severe diarrhea for which cocodiazine, 5 gr. every 6 hours, and intravenous fluids were ordered. Stool cultures at this time grew Pseudomonas Aeruginosa. On the following day the infant was in severe acidosis and additional parenteral fluids were administered. Two days later the infant was much improved and the cocodiazine was discontinued. The urine at this time showed 200 mgm. of albumin and few white blood cells.

The patient did fairly well until the 18th of September when urinalysis revealed turbid and bloody urine. There was 1500 mg. of albumin, many white blood cells, few red blood cells, few fine granular casts and a positive Benzidine test for blood. The urine culture on this date grew Pseudomonas Aeruginosa and a culture repeated on September 24, 1947 also grew Pseudomonas Aeruginosa. On September 19, 1947 the urine showed 200 mgms. of albumin, few white blood cells and many coarse granular casts. The urine was negative on the 20th of September and has remained so.

On September 19, 1947 the Kahn was reported as negative. The patient's urine remained normal, the blood count was within normal limits and the total protein had risen to 5.24 gms. per 100 cc. The patient was dismissed from the hospital on October 18, 1947.

DISCUSSION

This is a proven case of congenital syphilis which presents signs, symptoms and laboratory findings suggestive of an associated nephritis. Whether the edema, hypertension, albuminuria and hematuria can be attributed to syphilis or other causes (i.e. infection, toxins, etc.) is debatable.

Mitchell and Nelson[1] state that acute glomerulonephritis is uncom-

mon under three years of age. In the very young infant, glomerulonephritis is occasionally seen with congenital syphilis. Brenneman's Practice of Pediatrics[2] states "most instances of hemorrhagic nephritis under one year of age are due to syphilis."

Edema, which was the presenting complaint in this patient, is present in many congenital syphilitics and the outstanding feature of a few. It is, however, a more constant finding in acute nephritis. Whether the edema in syphilis is due to a primary hypoprotenemia or to a hepatitis associated with a low plasma protein is not known. It is well known that nephritics often show a lowered plasma protein level. The urine on admission to the hospital contained 500 mgm. of albumin and numerous granular casts; a repeat urinalysis four days later showed 150 mgm. of albumin and a rare red blood cell. These urinary findings were very similar to those found by Zampolsky and Mullins[3] in a two month old colored girl with congenital syphilis whose postmortem examination revealed "second stage glomerulonephritis." It is interesting to note that of 14 congenital syphilitics under one year of age admitted to Children's Hospital in the past two years three showed significant quantities of albumin in the urine and two of these showed red blood cells in the urine. In addition to the edema and abnormal urinary findings the blood pressure of this patient was recorded as 128/90. As there were no other complicating illnesses at the time of admission, the urinary findings, edema and hypertension have to be explained by either syphilis or nephritis or a combination of the two.

It is not the purpose of this paper to present this patient as a case of nephritis due to syphilis. The infant received the usual dose of penicillin for congenital syphilis with some improvement of the urinary findings at the end of treatment and normal urine on discharge. The hospital course was complicated by numerous episodes of diarrhea, some mild and some moderately severe. During one of these episodes the urine was grossly bloody and contained 1500 mgm. of albumin. This particular urine followed a course of cocodiazine which, however, had been discontinued 24 hours previously. The urine quickly returned to normal. It must be emphasized that both stool and urine cultures were positive for Pseudomonas Aeruginosa, normally a non-pathogen. It is conceivable that this patient had a pyelitis but on no occasion did any of the urine show clumped white blood cells.

On discharge from the hospital the patient was eating well and gaining weight and the laboratory findings of the urine and blood were within normal limits.

In conclusion, it is suggested that serologies be done by any examiner who finds abnormalities in the urine of a young infant who does or does not

appear edematous. To say that the nephritis even in the presence of a positive serology is due to syphilis cannot be substantiated but the association of albuminuria, hematuria, hypertension and a positive serology cannot be denied in this patient.

1. Mitchell and Nelson: Textbook of Pediatrics, p. 969.
2. Brenneman's Practice of Pediatrics, Vol. III, Chap. 28, p. 3.
3. Zampolsky, J., and Mullins, D. F.: American Journal of Diseases of Children, **69:** 163–172 (March) 1945.

EVENTRATION OF THE DIAPHRAGM

Case Report No. 108

Robert B. Sullivan, M.D. W. B. 46-8320

On September 10, 1947 a four month old white boy was admitted to Children's Hospital because of violent attacks of coughing during the preceding month.

Past history revealed that after an uneventful pregnancy the infant was born at term by a normal delivery. He weighed six pounds and three ounces. There was no neonatal cyanosis, jaundice, convulsions, or respiratory distress. He was bottle fed and feedings were taken slowly but well. Caloric and vitamin intake was adequate. His physical and mental development seemed normal and up until the age of three months he had no illnesses, injuries or operations. The parents and a three year old sister were well. No familial diseases were known.

Four weeks before admission the infant who appeared ostensibly well and manifesting no signs of an upper respiratory infection suddenly had an episode of violent coughing and gagging lasting for one to two minutes. There was no history of aspirated formula or other foreign body and there was no fever or vomiting. He recovered completely but from then on he had a daily, tight, rasping cough which occurred chiefly at night and was unaccompanied by whooping, vomiting or fever. His voice sounds remained unchanged. Pertussis was considered a diagnostic possibility. During the week preceding admission he had frequent coughing episodes during which time his neck and face became cyanotic. Shortly before admission the infant was seen by a pediatrician and was found to be fairly well nourished, afebrile, and in respiratory distress with moderate supra and infra-sternal retraction suggesting laryngeal or tracheal obstruction. There were no signs of infection and examination of the chest revealed loud tracheal wheezes and the absence of ectopic peristaltic sounds. The heart was thought to be displaced to the right and the left chest was dull posteriorly. The abdomen was not scaphoid and seemed normal. X-ray examination of the chest suggested either a diaphragmatic hernia or eventration of the diaphragm.

Drs. Edgar Davis and Roy Klepser explored the left hemithorax through an incision in the eighth intercostal space. The left lung was almost completely collapsed and the abdominal contents including the stomach and spleen could be seen through the left half of the diaphragm which was markedly eventrated and composed mainly of peritoneum and pleura with little evidence of a muscular component. This structure was incised

coronally and plicated antero-posteriorly so that there were three thick-thicknesses of tissue and the diaphragm was fixed at its normal level. The lung was fully re-expanded by positive pressure. Immediately postoperatively, an x-ray of the chest showed normal thoraco-abdominal relations. However, six days later the left side of the diaphragm was found to have returned to the level of the sixth rib posteriorly. Clinically the infant continued to be in moderate respiratory distress for ten days postoperatively

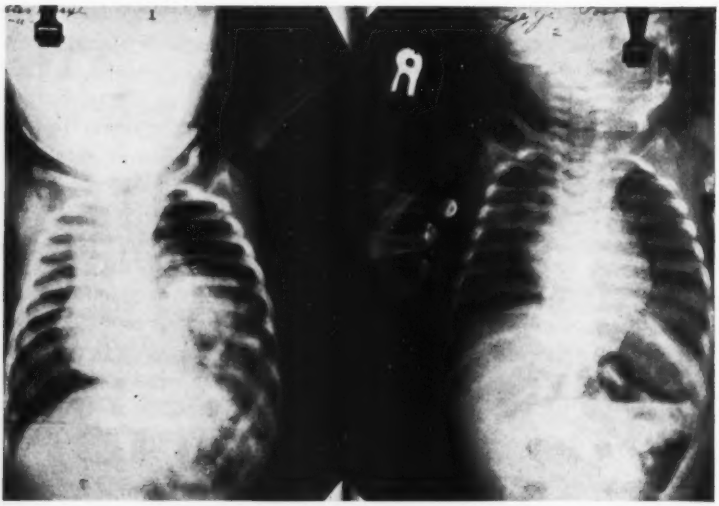

FIG. I (left). W. B.: Showing the smoothly eventrated diaphragm elevated to the third interspace on the left. The child was given barium by mouth and held in the upside down position and the stomach, splenic flexure and portion of the small intestine is seen pushing into the thorax displacing the heart somewhat to the right.

FIG. II (right). After the initial operation the abdominal viscera were restored to their normal positions and the chest appears relatively normal.

but thereafter, in spite of the x-ray evidence of a recurrence of the eventration, his respiratory function became practically normal and he was discharged.

During the next three months he remained unchanged but failed to sit up and was discovered to be blind and deaf. A diagnosis of cerebral agenesis was entertained.

When he was eight months old, he was re-admitted because of a sudden onset of intractable vomiting followed by respiratory distress. There was no evidence of a respiratory infection. The infant was dehydrated and his color was ashen. He was breathing rapidly and the left hemi-thorax was

hyperresonant anteriorly but breath sounds were poorly transmitted. An x-ray study showed the stomach and portions of intestine in the left chest. The thorax was again opened and the stomach, part of the large and small bowel, and the omentum were found to have herniated through a hole in the anterior line of the plicated diaphragm. These organs were reduced and the defect was closed from front to back with interrupted sutures. Since this operation there has been no respiratory distress during the ten month postoperative period. Unfortunately in addition to the patient's blindness

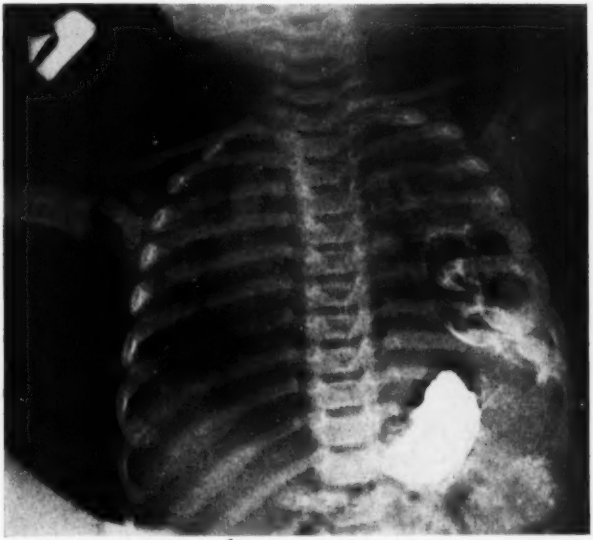

FIG. III. W. B.: Shows barium taken by mouth to be in the stomach and the stomach is in its normal positions. Barium by enema, however, reveals an herniation of the left side of the large intestine into the thorax.

and deafness he has had clonic convulsive movements of the lower extremities suggesting an associated marked anomaly of the central nervous system.

DISCUSSION

Eventration of the diaphragm is a condition in which one leaf is abnormally high. The usual causes are congenital malformation, trauma or disease of the phrenic nerve. It occurs more often on the left side and may cause little or no disability. If the eventration is marked, the abdominal contents may be so displaced that diaphragmatic hernia is simulated. The

mediastinum may be shifted and one lung compressed causing coughing, respiratory embarrassment and cyanosis. There may be decreased respiratory excursions over the involved side with hyperresonance and ectopic peristaltic sounds. The abdomen may be scaphoid. Signs of intestinal obstruction are more common in diaphragmatic hernia. X-ray examina-

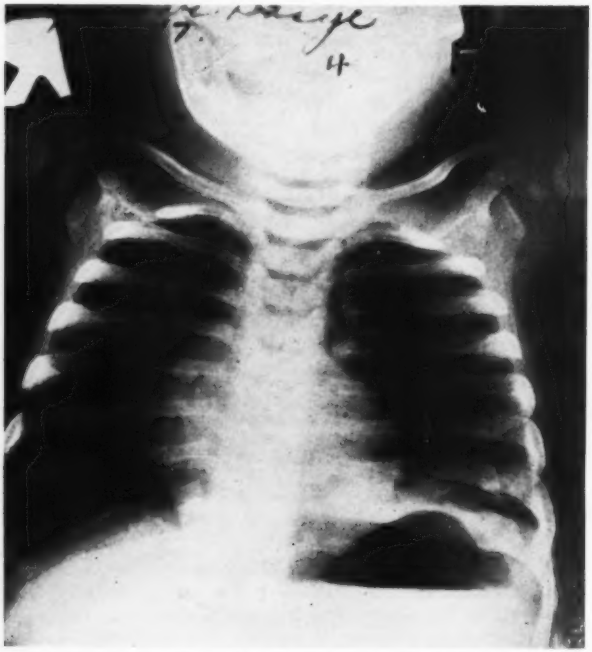

FIG. IV. W. B.: X-ray of the chest showing the abdominal viscera to have again been restored to their normal positions, There is no abnormality of the chest at this time.

tion and fluoroscopy of the chest with and without the ingestion of barium will demonstrate the displaced viscera. If the diaphragmatic shadow can be clearly seen arching over the abdominal contents, eventration can be differentiated from herniation. The only corrective treatment is surgical and both thoracic and abdominal approaches are used. An attempt is made to establish a strong partition between the thorax and the abdomen at the normal level. The loss of diaphragmatic motility does not prevent good respiratory function.

MENINGOCOCCEMIA: REPORT OF A CASE COMPLICATED BY ULCERATION OF SKIN LESIONS

Allan B. Coleman, M.D.

A four year old negro girl was admitted to the hospital because of fever and abdominal pain of 18 hours duration.

The patient awoke on the morning of admission complaining of intermittent, crampy periumbilical pain. There was no nausea or vomiting. Fever was noted by the parent. During the next 12 hours she was drowsy, and refused food, but took liquids well. About one hour before admission to the hospital she had a brief generalized convulsion, and remained semistuporous afterward. She had a loose, foul smelling stool shortly before admission.

The birth, feeding and developmental histories were normal. Past illnesses included measles, chickenpox and mild diarrhea. The family history was non-contributory.

Physical examination revealed a well developed and nourished four year old appearing seriously ill. She was restless and muttered incoherently. The temperature was 102°F., pulse 158 and respirations 36 per minute.

The skin was hot and dry and there were a few red to pink macules scattered over the chest and abdomen, which did not blanch with pressure. Small anterior cervical lymph nodes were palpable. No petechiae were seen on the mucous membranes. The deep reflexes were sluggish to absent; superficial reflexes were absent. Equivocally positive Kernig and Brudzinski signs were noted.

Initial studies showed a white blood cell count of 9,100 per cubic millimeter, of which 76% were polymorphonuclear cells (including 40 stab forms and 8 metamyelocytes). The urine was concentrated and contained 60 mgms. of alnumin per 100 cc. A blood culture and smears and cultures from the skin lesions contained meningococci. Spinal fluid obtained upon admission was entirely normal. Blood Kahn and Mazzini tests were negative, as was a Mantoux test with second strength P.P.D. tuberculin. The organism isolated by blood culture was inhibited by 0.125 units of penicillin per cubic centimeter, *in vitro*; that from the skin lesion cultures was inhibited by 0.175 units of penicillin per cubic centimeter.

During the first 12 hours after admission to the hospital the initial skin lesions became hemorrhagic and crops of pink papules appeared on the trunk and extremities.

Administration of sulfadiazine and penicillin, by parenteral routes, was begun soon after admission. The temperature (see figure 1) rose to 103.4°F. and then fell by rapid lysis, reaching normal during the second

hospital day. The patient became rational on the third hospital day. Subsequently the temperature rose to 101°F. on the fifth day and ranged between 100° and 102°F. during the next 10 days. The remaining hospital course was essentially afebrile, except for an occasional afternoon rise in temperature to 100.4°F. during the fourth week.

Sulfadiazine was discontinued on the sixth day because of hematuria, but the penicillin was continued.

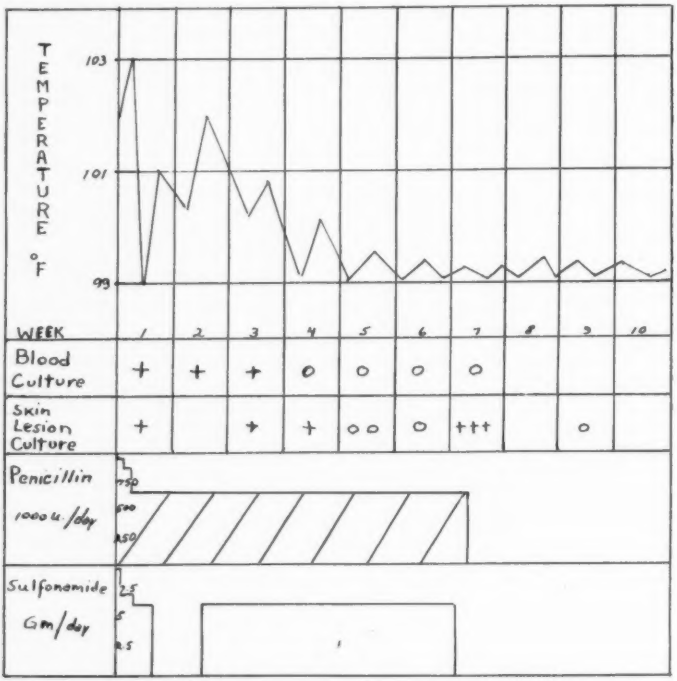

FIG. 1

Two weeks after admission it was noted that many of the skin lesions were breaking down to form shallow ulcers; meningococci were isolated from these ulcers. A blood culture drawn on the same day was positive for meningococci. A course of sulfadiazine and sulfathiazole together was started and continued for the next three weeks. The blood sulfonamide level ranged between 7.5 and 26.9 milligrams per 100 cubic centimeters. Concurrently, the skin lesions were treated with penicillin ointment and sulfadiazine ointment.

On the 36th hospital day all medication was discontinued. At that time only two of the ulcers had failed to heal completely. They were culture-negative for meningococci.

Blood cultures drawn on five occasions after the 24th day were sterile.

On the 44th, 47th and 56th hospital days positive cultures for meningococci were again obtained from the two unhealed skin lesions. Under local therapy with "Furacin" ointment these lesions healed completely, and on the 65th day an aspiration culture from them was sterile.

The patient was discharged on the 70th hospital day. When last seen, two months later, she was gaining weight and looked well. The skin lesions were covered by firm scar tissue. A blood culture was sterile and the erythrocyte sedimentation rate was within normal limits.

DISCUSSION

Meningococcemia has become a relatively common disease in recent years because of increasing awareness of it on the part of clinicians. Many case reports have appeared in the literature.

In the past 5 years (January, 1943 through October, 1947) there have been 40 cases of meningococcemia admitted to the Children's Hospital among 34,153 consecutive admissions—an admission rate of approximately 0.1% and an average of 8 cases per year.

A brief review of current literature indicates that the most frequent complications of meningococcemia are meningitis, Waterhouse-Fridrichsen Syndrome and arthritis in that order[1, 2]. Panophthalmitis[2], iritis[3], myocarditis[4] and ulceration of purpura[4] are less common.

The patient presented here showed the unusual feature of ulcerative purpurae, persistently culture-positive for meningococci of low penicillin resistance, despite prolonged systemic administration of penicillin and two sulfonamides in high dosage. Penicillin and sulfadiazine ointments caused only transient sterilization of the ulcers.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: Dr. E. Clarence Rice
Assisted by: Dr. Harold Bischoff
Dr. Adrian Recinos
By Invitation: Dr. Sidney Ross
Harold Bischoff, M.D.

A 15 month old white male was admitted to the Children's Hospital for the first time on March 31, 1947 with the following symptoms: he was unable to hold up his head, sit alone or walk and never attempted to learn to talk. The parents felt that the child developed normally during his first six months of life. He was at that time able to sit alone for a few moments, hold his bottle and move around in his crib. Since about six months of age, however, he had gradually become less active and would scarcely try to grasp a toy. He seemed limp and weak when he was lifted from his crib, and he was unable to drink from a glass. There was a tendency towards constipation.

The child was full term, delivered spontaneously and weighed 6 pounds 4 ounces. He received artificial feeding with supplemental orange juice. He was given diphtheria toxoid and a smallpox vaccination. The infant had had no serious illnesses and there was no known injury. There was one sibling and the mother and father were living and well. They were unaware of any familial diseases including mental retardation.

Physical examination revealed a fairly well developed, well nourished white male with a peculiar little cry and expressionless face. The child lay on his back, his lower extremities were externally rotated, his arms abducted and externally rotated. He seemed apathetic to external stimulae. His weight was 17 pounds 5 ounces. The fontanelle was large but depressed. The inner canthus of each eye was large suggesting mongolism. The pupils of the eyes were oval, equal and reacted to light. The nose and ears were normal. There were 8 incisors and 4 molars. The tonsils were enlarged but not inflamed. The cardiovascular and respiratory systems were normal. The abdomen was negative on inspection and palpation and no abdominal reflexes could be elicited. Spasticity was present to a slight degree in both legs and arms. Movements of the extremities were present but were weak while the tendon reflexes were hyperactive. Fundoscopic examination revealed a few areas of reddish discoloration around the maculae; the vessels were normal and there was no evidence of papilledema. The laboratory reported a negative urinalysis, 12.5 gms. of hemoglobin, 3,860,000 erythrocytes, 7,200 leucocytes and a normal differential. The parents took the patient from the hospital before other studies were done.

The child was readmitted to the hospital on June 4, 1947. Since his last admission there had been a steady progression of weakness and apathy. He was unable to see, did not recognize his parents' voices and he had been losing weight. He refused to eat or take fluids.

Physical examination at this time revealed a 17 month old male who appeared critically ill. He was cyanotic, dehydrated and extremely emaciated. The lungs were clear. The cardiac rate was rapid and the rhythm irregular. The abdomen was flat and atonic. No other abnormalities were noted.

The laboratory reported a slightly cloudy urine with a trace of glucose and a few white blood cells. There was 9.5 grams of hemoglobin, 3,020,000 erythrocytes and 9,600 leucocytes with 77% neutrophiles, 22% lymphocytes and 1% monocytes. An electrocardiogram showed sinus tachycardia and upright T waves in all leads. The child was given intravenous fluids but expired several days later. An autopsy was done.

DISCUSSION

Sidney Ross, M.D.: For purposes of discussion it might be well to divide the presenting symptomatology in this case into three broad categories including (1) mental deterioration, (2) blindness and (3) neuromuscular weakness with the object of discussing the diagnostic possibilities in each group.

Under the heading of mental deterioration, there are several possibilities to be considered. Birth injury whether due to prenatal, paranatal or postnatal difficulties would be a consideration. However, the parent's history that the child developed normally during the first 6 months would militate against the diagnosis of birth injury whether due to anoxemia or trauma since the manifestations of birth injury would in all likelihood appear earlier than 6 months of age. It is well to add that brain defects and not birth injury are responsible for most of the cases of mental retardation. It has been estimated that about three fourths of those infants with birth injuries who survive the first week of life recover quite completely without any overt evidence of retardation while the remaining 25% gradually improve to the point where they can walk, talk and dress themselves even though they may never achieve normalcy. The chronology of events, however, usually is in the direction of improvement from birth while in the case under discussion, the process was quite the reverse, i.e. a presumably normal child who at the end of 6 months began to gradually show signs of retardation and mental deterioration. This sequence of events would be more in keeping with a constitutional abnormality or brain defect rather than a birth injury. Other factors militating against a diagnosis of birth injury include the absence of any evidence of postnatal cyanosis, convulsions,

irregular breathing, hypotonia or difficulties associated with the delivery of the infant.

Post-natal infection involving the central nervous system can presumably be ruled out by the lack of any history of an acute infectious process.

Kernicterus following erythroblastosis fetalis could conceivably produce subsequent mental retardation as a later manifestation. Stiller[1] recently reported a 15% incidence of kernicterus in a series of 29 living cases of erythroblastosis at this hospital. Unlike the case under discussion, however, the symptoms related to kernicterus are more frequently referable to basal ganglion involvement, viz. spasticity of an extrapyramidal type, together with athetoid and choreiform movements. In addition there is no mention of any Rh incompatibility in the case history. A further point against this possibility is the relative infrequency of erythroblastosis in a second living child. In my experience on a large newborn service at the Naval Medical Hospital at Bethesda I have encountered few instances of erythroblastosis occurring in a second infant except in cases where an Rh negative mother has been additionally sensitized by an Rh positive transfu ion or a previous still birth or miscarriage carried beyond the sixth month.

It is well to consider maternal rubella in every case of mental retardation in the light of our more recent knowledge. Congenital cataracts and cardiac lesions are the more common manifestations but mental retardation may coexist or be present alone in such cases. Since there is no mention in the protocol of German measles during the mother's first trimester, however, we can presumably eliminate this possibility.

Mention is made in the physical examination of the appearance of the "large inner canthus of each eye suggesting mongolism." However, one would strongly doubt that the infant was a mongol in the absence of any of the other usually noted stigmata. Similarly cretinism can be ruled out in view of the absence of compatible clinical manifestations and the course of the disease. Congenital hydrocephalus, toxoplasmosis, amyotonia congenita and progressive spinal muscular atrophy (Werdnig-Hoffman type) may be mentioned and excluded on the basis of insufficient evidence.

Other diagnostic possibilities include the xanthomatoses such as Neiman-Pick's disease and Tay-Sach's disease or familial amaurotic idiocy. Both may occur in infancy and are accompanied by the three cardinal manifestations noted in the case history, i.e. neuromuscular weakness, blindness and idiocy. In the protocol there is a notation that the fundoscopic examination of the eyegrounds revealed a "few areas of reddish discoloration around the macula" and no specific mention is made of a cherry red spot which is one of the more pathognomonic features noted with both Nieman-Pick and more particularly Tay-Sach's disease. However, occasionally one may

find macular changes in these xanthomatoses which may be regarded as equivalents of the cherry red spot. These may have the appearance of a reddish macula surrounded by a pigmented ring. The macular lesions described in the case under discussion would conceivably also be designated as an equivalent. As a matter of fact, cases of Tay-Sach's disease have been described in which no macular changes were observed.

No mention is made in the history of the race of the patient. In view of the fact that both Tay-Sach's and Nieman-Pick's disease are much more common in Jewish infants it would be a point of diagnostic importance.

Dr. Bischoff: The infant was not Jewish.

Dr. Ross: That does not necessarily rule out the diagnosis of either Tay-Sach's or Nieman-Pick's disease. Admittedly it is rare to find the disease in non-Jewish children. However, Roos[2] in a review of the literature found 2 cases of Tay-Sach's disease confirmed at autopsy occurring in non-Jewish infants and reported a third case of his own which occurred in an infant of pure Norwegian stock. Nieman-Pick's may occur more frequently in non-Jews since of the 60 cases reported in the literature to date, only one half were Jewish.

Tay-Sach's disease usually shows a strong familial tendency. However, there is no indication of its familial occurrence in the case history. The sibling was described as being in good health and the parents were unaware of any mental retardation in the immediate family. However, this does not preclude a diagnosis of Tay-Sach's disease since it is not transmitted according to any simple Mendelian law and the precise nature of the mode of inheritance still remains abstruse. It has been noted that some children in a family where the morbid factor of Tay-Sach's disease is present may escape completely and remain perfectly normal. Thus Herman[3] describes a case of Tay-Sach's disease occurring in one of twins, the other twin remaining completely well. It is quite conceivable that if the parents of this infant had had more than two children, its familial tendency might have been more in evidence.

The course of the illness is quite in keeping with one of the cerebromacular degenerative entities such as Tay-Sach's or Nieman-Pick's disease. We have an ostensibly healthy 6 months old infant insidiously manifesting a progressive weakness and torpor, mental deterioration, blindness and finally death at the age of 17 months. The first symptoms consisting of weakness and listlessness usually appear between 6 to 9 months in the average case of Tay-Sach's as it did here followed by physical and mental retrogression and subsequent amaurosis. Occasionally, some cases may run a protracted course lasting 3 to 4 years, but in the usual instance death follows a 12 to 18 month progressively downhill course. In this case, the duration was 11 months.

There are many clinical points of similarity between Nieman-Pick's and Tay-Sach's disease including its occurrence chiefly in Jewish infants, mental and physical deterioration and blindness; in addition a cherry red spot in the macula area has been occasionally described in Nieman-Pick's disease although less frequently than in Tay-Sach's disease. However, the protocol carries no mention of a demonstrable hepato-splenomegaly which would tend to make Nieman-Pick's a less likely possibility than Tay-Sach's disease.

In conclusion, I would guess that Tay-Sach's disease (or amaurotic familial idiocy) represents the most likely diagnosis in spite of the fact that the infant is non-Jewish, that there is no familial component demonstrable and that the typical cherry red spot was not observed.

PATHOLOGICAL DISCUSSION

E. Clarence Rice, M.D.: At necropsy the patient was found to be poorly nourished. The noteworthy findings were in the central nervous system. The convolutions were slightly flattened and on section the lateral ventricles appeared to be somewhat larger than normal. On microscopic examination the ganglion cells are found to be prominent due to swelling and the Nissl granules have disappeared from the periphery. These cells have a granular appearance and the nuclei are not changed to any great degree. There is some proliferation of astrocytes. The changes noted are those seen in amaurotic family idiocy (Tay-Sach's disease).

If we could examine the eye microscopically, degeneration of the ganglion cells of the retina in the macular region would be found to be responsible for the exposure of the choroid, this being the reason that one sees the cherry red spot which is pathognomic of this disease.

The changes in the central nervous system are not unlike those seen in involvement of the brain in Nieman-Pick's disease. If such changes are noted in the latter disease there are also visceral lesions which are never seen in amaurotic family idiocy. Both appear to be due to a condition in which the metabolism of lipoids has become unbalanced.

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